REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 42-57 are pending. Claim 43 has been canceled and claims 42, 51 and 52 have been amended in a manner that more clearly defines certain subject matter encompassed by applicants' invention. Claims 44-46 have been amended solely to correct what would otherwise be an improper dependency on a canceled claim. Support for the amendments may be found in the specification, for example, at page 6, lines 14-18; at page 12, lines 16-23; at page 15, lines 9-28; page 17, lines 7-26; page 19, lines 19-25; page 20, lines 20-30; page 39, line 11 through page 40, line 20; page 42, line 14 through page 45, line 13; and in the Examples (*e.g.*, pages 48-55, 60-68, 70-75). No new matter has been added.

Attached hereto is a marked-up version of the changes made to the claims by the current Amendment, the first page of which is captioned "Version with Markings to Show Changes Made."

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 42-52 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not adequately described in the specification. More specifically, the Action asserts that the specification fails to provide a representative number of species to describe the claimed genus of isolated adenine nucleotide translocator (ANT) polypeptides, and that structural and functional properties shared by the disclosed species, or by fragments and variants thereof, are not disclosed.

Applicants respectfully traverse these grounds for rejection and submit that, for reasons previously made of record, the description of the claimed invention in the specification is sufficient to reasonably convey to a person having ordinary skill in the art that the applicants, at the time of filing the application, had possession of the claimed invention. Nevertheless, without acquiescing in the present rejection, but solely for purposes of advancing the prosecution of the instant application without prejudice to any related continuation, divisional, continuation-in-part,

reissue or reexamination application, applicants note that as amended herein, the present invention is directed, according to certain presently claimed embodiments, to an isolated human adenine nucleotide translocator polypeptide that is capable of binding an ANT ligand and that is produced by a method of culturing a host cell having a recombinant expression construct that has at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide.

As noted in the specification, for example, at page 4, lines 18-24, and at page 12, lines 6-12, and as discussed in greater detail below, the present invention provides isolated human ANT polypeptides that are neither disclosed nor contemplated by the prior art where, *inter alia*, problems related to ANT solubility, toxicity, and/or a tendency to accumulate in inclusion bodies (*e.g.*, Miroux et al., 1996 *J. Mol. Biol.* 260:289, at pages 290-291 and Table 1) all precluded the preparation of the claimed ANT polypeptides with any reasonable expectation of success, even where the nucleic acid sequences of cDNAs encoding at least three human ANT isoforms have been known since 1989 (specification at page 15, lines 15-26).

Applicants respectfully submit that, in view of the prior art, the instant specification more than adequately describes a number of known human adenine nucleotide translocator polypeptide isoforms, and that the structure of this family of polypeptides is highly conserved (*see, e.g.*, specification, page 12, lines 16-26; page 15, line 7 through page 16, line 2; page 17, lines 4-29; see also, *e.g.*, Fiore et al., 1998 *Biochimie* 80:137, at page 138, column 2 under "Genomic Structure of the ADP/ATP Carriers" and page 139, Figure 1). Further, the instant specification abundantly teaches how to make and use a claimed human ANT polypeptide that is capable of binding an ANT ligand. For example, isolated recombinant human ANT polypeptides that are capable of binding ANT ligands, the ANT ligands themselves, and their use in ANT-binding assays are described at page 39, line 11 through page 45, line 13; and in the Examples (pages 48-93). ANT-mediated stoichiometric exchange of ATP and ADP across the inner mitochondrial membrane is described, for instance, at page 13, line 27 through page 14, line 1; ATP binding to an isolated human ANT3 polypeptide is described at pages 88-90. As another example, descriptions of how to make and use isolated human ANT3 polypeptides that are capable of binding to an ANT ligand are also provided at pages 91-93 of the instant specification, where binding to ANT ligands that are atractyloside derivatives is demonstrated.

Thus, as disclosed in the specification and recited in the claims, the present application establishes human adenine nucleotide translocator polypeptides that are capable of binding to an ANT ligand. Accordingly, in view of the number of disclosed species of ANT polypeptides (*see, e.g.*, SEQ ID NOS:31-33), a person having ordinary skill in the art would recognize that applicants were in possession of the attributes common to the members of the genus. Additionally, applicants respectfully submit that the instant specification conveys to a person having ordinary skill in the art that the applicants had, at the time of filing, possession of isolated human ANT polypeptides, or variants or fragments thereof, which are capable of binding to an ANT ligand. As applicants have previously noted, the instant specification teaches that a "fragment" includes any ANT polypeptide that retains essentially the same biological function or activity as an ANT polypeptide (*e.g.*, specification, page 19, line 28 through page 20, line 3). Moreover, the biological functions or activities of ANT polypeptides or variants or fragments thereof are well known in the art, such as binding ANT ligands (*see, e.g.*, specification, page 15, lines 1-6; and Fiore et al., page 138, column 1, last paragraph). As also discussed above, the instant specification teaches a person having ordinary skill in the art how to analyze human ANT polypeptides structurally (*e.g.*, specification, page 20, line 20 through page 21, line 8) and in functional assays of ANT ligand binding (*e.g.*, specification, Examples 10, 11, and 12). Thus, based on the instant specification, a person having ordinary skill in the art (i) would recognize the presence of the claimed isolated human ANT polypeptide, (ii) could clearly identify the presence of a variant or fragment thereof, and (iii) would be able readily to determine whether such a polypeptide is capable of binding to an ANT ligand.

Therefore, applicants respectfully submit that the instant specification and claims adequately describe the claimed invention and, consequently, that the present application satisfies the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, applicants respectfully request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102(a)

The Examiner maintained the rejection of claims 42-46 under 35 U.S.C. § 102(a) as being anticipated by Marzo et al. (*Science 281*:2027-2031, 1998). More specifically, the Action asserts that Marzo et al. teach a purified human ANT2 protein. The Action alleges further

that applicants' invention is the same product as that described by Marzo et al., but is merely derived via an alternative process.

Applicants respectfully traverse this ground for rejection. Applicants submit that the cited reference fails to meet every limitation of the instant claims and, therefore, Marzo et al. fail to anticipate the claimed invention. As disclosed in the specification and recited in the claims, the instant invention is directed in pertinent part to an isolated human adenine nucleotide translocator polypeptide that is capable of binding to an ANT ligand and that is produced by a method of culturing a host cell comprising a recombinant expression construct that has at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide. Applicants respectfully submit that Marzo et al. fail to teach an isolated human adenine nucleotide translocator that is produced recombinantly, nor do Marzo et al. provide an isolated human ANT polypeptide that is capable of binding an ANT ligand.

Marzo et al. merely describe recombinant expression of a 55 amino acid domain of human ANT2 in an intact yeast dihybrid cell system (Marzo et al., Figure 4B at p. 2030; note 22 at page 2031), and the teachings of Marzo et al. in this regard are limited to detection of protein-protein interactions in such intact cells. Applicants therefore respectfully submit that Marzo et al. fail to teach a recombinant, *isolated* human ANT polypeptide which, as disclosed in the instant specification and recited in the instant claims, is *capable of binding an ANT ligand.* The Action does not specifically point to any teaching by Marzo et al. that is directed to an isolated human ANT polypeptide that is capable of binding an ANT ligand, wherein the ANT polypeptide is produced by a method comprising culturing a host cell comprising a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide.

Moreover, applicants are aware of no prior art disclosure relating to the subject matter of the instant claims (*i.e.*, a recombinantly produced human ANT polypeptide that is capable of binding an ANT ligand, as provided by the instant application). On this point, and contrary to the assertion in the Action, applicants respectfully submit that the *process* utilized to arrive at the instant polypeptide is novel, where an isolated recombinant human ANT polypeptide having the recited features is absent from the prior art. Therefore, applicants submit that the claimed product is not anticipated by the prior art.

Additionally, insofar as the cited reference is silent regarding whether the recombinant 55 amino acid human ANT2-derived polypeptide expressed in, but *not* isolated from, yeast, as disclosed by Marzo et al., is capable or incapable of binding an ANT ligand, applicants submit that the subject matter of the instant claims is patentably distinct from the product disclosed in the prior art. Applicants therefore submit that Marzo et al. fail to teach an isolated human ANT polypeptide that is capable of binding an ANT ligand and that is produced by culturing a host cell having a *recombinant* expression construct comprising a *regulated* promoter operably linked to a nucleic acid encoding the ANT polypeptide, as is provided by the present invention. Accordingly, applicants respectfully submit that the instant invention is readily distinguished over Marzo et al., and request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

The Examiner also rejected claims 42-46 under 35 U.S.C. § 102(a) as being anticipated by Fiore et al. (*Biochimie 80*:137-150, 1998). More specifically, the Action asserts that the fact that Fiore et al. do not isolate a human ANT polypeptide does not obviate the fact that the human ANT polypeptide sequence is disclosed in the prior art.

Applicants respectfully traverse this ground for rejection and submit that Fiore et al. fail to anticipate the claimed invention. It is well settled that for a reference to anticipate a claim under 35 U. S. C. §102, the reference must teach every limitation of the claim. In the instant case, the Action concedes that Fiore et al. fail to provide an *isolated* human ANT polypeptide according to the present invention. By way of contrast, the present invention is directed in pertinent part to an isolated human ANT polypeptide that is capable of binding an ANT ligand, as discussed above. Applicants therefore respectfully submit that the novelty rejection over Fiore et al. is inappropriately applied.

As described in the specification, for example, at page 21, lines 9-15, an "isolated" ANT polypeptide will include an ANT polypeptide that is removed from its original environment. Fiore et al. merely teach that known ANT polypeptide *sequences* have been deduced from nucleotide sequences (page 138, column 2, lines 1-3 under "Genomic Structure of the ADP/ATP Carriers"), but Fiore et al. fail to disclose actual isolation of any human ANT polypeptides, nor of any human ANT polypeptide that is capable of binding an ANT ligand, nor of any human ANT polypeptide that is produced by culturing a host cell comprising a

recombinant expression construct comprising a regulated promoter operably linked to an ANT-encoding nucleic acid. Applicants therefore submit that Fiore et al. fail to teach or suggest the subject matter of the instant claims.

Accordingly, applicants respectfully submit that the instant invention is readily distinguished over Fiore et al., and request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

The Examiner rejected claims 43-57 under 35 U.S.C. § 103(a) as being unpatentable over Fiore et al. (*Biochimie 80*:137-150, 1998) in view of Rosenberg (*Protein Analysis and Purification: Benchtop Techniques*, Birkhäuser, Boston, pp. 335-347, 1996). More specifically, the Action asserts that it would have been obvious to purify an ANT protein using a polyhistidine tag as disclosed by Fiore et al., and further that it would have been obvious to try to improve on such purification methods by preparing ANT fusion proteins according to the teachings of Rosenberg. The Examiner also rejected claims 43-50 and 52-55 under 35 U.S.C. § 103(a) as being unpatentable over Adrian et al. (*Molecular and Cellular Biology 6*(2):626-634, 1986), in view of Fiore et al., alleging that a person having ordinary skill in the art would have found it obvious to substitute human or animal ANT instead of the disclosed yeast ANT in order to study mitochondrial localization sequences in human or animal ANT.

Applicants respectfully traverse these grounds for rejection. The cited references, alone or in combination, fail to teach or suggest an isolated human adenine nucleotide translocator polypeptide that is capable of binding an ANT ligand, or an isolated human or animal adenine nucleotide translocator fusion protein comprising an adenine translocator polypeptide fused to at least one additional polypeptide sequence. As noted above, Fiore et al. disclose several ANT polypeptide *sequences* that have been deduced from nucleotide sequences, but Fiore et al. fail to teach or suggest actual isolation of any human ANT polypeptide, or of any human or animal ANT fusion proteins. As discussed in greater detail below, applicants also submit that the present invention is nonobvious when secondary factors, and in particular the identification of a long-felt need and the failure of others, are considered.

Applicants respectfully submit that it is well established that an assertion that it would have been "obvious to try" to improve on the prior art methods, such as the assertion found at page 6, lines 4-7 of the Action, cannot be regarded as a conclusory finding that the claimed invention is obvious, and fails to support a *prima facie* case of obviousness. *In re Eli Lilly & Co.*, 902 F.2d 943; 14 USPQ2d 1741 (Fed. Cir. 1990). Similarly, applicants submit that the Action employs inappropriate and selective hindsight where the allegation of obviousness is asserted to derive from a reason or suggestion in the art other than knowledge provided by applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469; 5 USPQ2d 1529 (Fed. Cir. 1988). For reasons already made of record, applicants submit that Fiore et al. fail to teach or suggest the instant invention, and that Rosenberg, alone or in combination with any knowledge in the art, is merely a general reference describing the construction and use of fusion proteins but which fails to remedy the deficiencies of Fiore et al. Rosenberg thus fails to provide any teaching or suggestion that could have motivated a person having ordinary skill in the art to arrive at the claimed isolated human adenine nucleotide translocator polypeptides and ANT fusion polypeptides, with a reasonable expectation of success.

In particular, the Action fails to provide specific reasoning in support of the assertion that the present invention would have been obvious at the time of filing the instant application, given the level of ordinary skill in the art. By way of contrast, applicants submit that if anything, the state of the art pointed away from arriving at the present invention with any reasonable expectation of success. For example, based on the teachings of Miroux et al. (1996 *J. Mol. Biol.* 260:289), a copy of which is enclosed for the Examiner's convenience, applicants submit that a person having ordinary skill in the art would have understood that recombinant expression of an ANT polypeptide is hardly a routine matter. More specifically, Miroux et al. describe efforts to express various recombinant proteins, including mammalian ANT, in a bacterial expression system. Multiple problems are described with regard to efforts to express recombinant ANT, including toxicity to host cells, poor solubility of the recombinant product and accumulation of recombinant ANT in inclusion bodies (*e.g.*, Miroux et al., 1996 *J. Mol. Biol.* 260:289, at pages 290-291 and Table 1), which applicants submit would be recognized by those familiar with the art as a form amenable neither to ready isolation nor to functional binding interactions with an ANT ligand. Applicants therefore respectfully submit that it would be

misguided to believe that the person having ordinary skill in the art at the time of the present application knew, with a reasonable expectation of success, how to arrive at the instant invention.

For the same reasons applicants also respectfully submit that Adrian et al. in view of Fiore et al. would not render the present invention obvious. The disclosure of Adrian et al. is limited to a determination of whether yeast ANT shares mitochondrial targeting sequence motifs with other typical mitochondrial proteins, but Adrian et al. fail to contemplate in any way the recombinant expression of human ANT polypeptides that are capable of binding to an ANT ligand, or of human or animal ANT fusion proteins, according to the present invention. The Action alleges that a person having ordinary skill in the art would have found it obvious to substitute human or animal ANT instead of the disclosed yeast ANT in order to study mitochondrial localization sequences in human or animal ANT, but applicants respectfully submit that such an allegation is beside the point, where Adrian et al. are concerned only with subcellular localization targeting motifs but the present invention is not so limited. Furthermore, applicants submit that the cited references alone or in combination fail to suggest that recombinant ANT expression could be comparably achieved if human or animal ANT sequences were substituted for the yeast sequences of Adrian et al. Thus, where the prior art failed to suggest to the person having ordinary skill in the art that the presently claimed ANT polypeptides should be made according to the present invention, and where, for reasons discussed herein, such a skilled artisan would not have found a reasonable expectation of success in the prior art, applicants submit that *prima facie* obviousness has not been established. *See, e.g., In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants also respectfully submit that the present invention is nonobvious when "secondary" factors, and in particular the identification of a long-felt need and the failure of others, are considered. It is well established that considerations such as long-felt but unsolved needs, and the failure of others to arrive at applicants' invention, are not only relevant to the obviousness inquiry, but must be considered when present. *Custom Accessories Inc., v. Jeffrey-Allan Industries Inc.*, 807 F.2d 955; 1 USPQ2d 1196 (Fed. Cir. 1986); *Ryko Manufacturing Co. v. Nu-Star Inc.*, 950 F.2d 714, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991).

Hence, and as noted above, applicants respectfully submit that where cDNA sequences encoding a human ANT polypeptide were known as early as 1987, and where

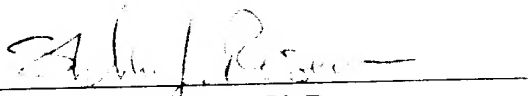
recombinant protein expression methods were established well before 1987, a long-felt need for reliable expression of ANT polypeptides was present at the time of filing the instant application in 1998. In addition, the attention directed to ANT polypeptides by numerous investigators, as evidenced by the prior art references cited throughout the instant specification (*e.g.*, page 15, lines 12-26; pages 39-40; Fiore et al.; and elsewhere) makes clear the desirability of being able to express recombinant human ANT that is capable of binding an ANT ligand. Moreover, and as stated above, applicants are unaware of any successful production by others of an isolated recombinant human ANT polypeptide that is capable of binding an ANT ligand, or of isolated ANT fusion proteins, according to the instant invention. In view of the absence of any such disclosures from the prior art, and further in view of unsuccessful efforts to express recombinant ANT in a useful form (*e.g.*, Miroux et al., *supra*), applicants therefore respectfully submit that the present invention is nonobvious when such secondary considerations are taken into account.

Applicants therefore respectfully submit that the Action has not set forth a *prima facie* case of obviousness. As discussed above, the cited references fail to provide a suggestion or motivation for a person having ordinary skill in the art to modify or combine the prior art teachings to arrive at the claimed invention with a reasonable expectation of success, and secondary considerations clearly show the invention to be non-obvious. Accordingly, applicants respectfully request that this rejection be withdrawn.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If the Examiner does not believe the claims are allowable for any reason, the Examiner is encouraged to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosure:
Copy of Miroux et al. (1996 *J. Mol. Biol.* 260:289)

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Version with Markings to Show Changes Made

42. (Twice Amended) An isolated human adenine nucleotide translocator polypeptide that is capable of binding an ANT ligand and that is produced by a method comprising culturing a host cell comprising a recombinant expression construct comprising at least one regulated promoter operably linked to a nucleic acid encoding the adenine nucleotide translocator polypeptide.

44. (Amended) The isolated polypeptide of claim 42 [43] wherein the human adenine nucleotide translocator polypeptide is recombinant ANT1 or a variant or fragment thereof.

45. (Amended) The isolated polypeptide of claim 42 [43] wherein the human adenine nucleotide translocator polypeptide is recombinant ANT2 or a variant or fragment thereof.

46. (Amended) The isolated polypeptide of claim 42 [43] wherein the human adenine nucleotide translocator polypeptide is recombinant ANT3 or a variant or fragment thereof.

51. (Amended) An isolated human adenine nucleotide translocator fusion protein comprising an adenine translocator polypeptide fused to at least one additional polypeptide sequence cleavable by a protease, said adenine nucleotide translocator polypeptide being capable of binding an ANT ligand and separable from the fusion protein by cleavage with the protease.

52. (Amended) An isolated adenine nucleotide translocator fusion protein comprising a first polypeptide that is an animal adenine translocator polypeptide that is capable of binding an ANT ligand and that is fused to at least one additional polypeptide sequence.